# A FATAL CASE OF DELAYED HYPERSENSITIVE (ANAPHYLACTIC) REACTION TO A TEST DOSE OF VASIODONE

BY

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Received December 3, 1949

The following account of an anaphylactic phenomenon is considered to be sufficiently unusual to be worthy of record.

The patient was a mentally subnormal girl, aged 10 years, who reported to the clinic in September 1949. She had been a difficult feeder in infancy but had caught up to normal weight at two years and at the time of examination her height and weight were both normal. Her physical activities were not greatly restricted. She was able to play quite well with other children though inclined to lag behind them. Her intelligence quotient was 64 per cent. There was no cyanosis, no clubbing, no history of convulsions, no palpitation, and no undue dyspnœa. Red blood count was 4,870,000 per cmm., hæmoglobin 13·5 g. per 100 ml. The brachial blood pressure was 116/60. The cardiac impulse was in the fifth space, 6·5 cm. from the mid-line. There was a grade-two systolic murmur audible over the whole præcordium and conducted up the carotid arteries and through to the back. There was no accentuation of the pulmonary second sound. X-ray studies carried out by Dr. N. Klein showed a transverse diameter of the heart of 12·5 cm. (cardio-thoracic ratio 60), enlargement of both ventricles, a very slight hilar dance, and increased size and pulsations of the pulmonary artery which bulged posteriorly into the retrocardiac space. The electrocardiogram showed evidence of some myocardial changes and a probability of right ventricular hypertrophy.

The diagnosis could not be determined with certainty and was considered to rest between patent ductus arteriosus, auricular or ventricular septal defect, or common atrioventricular opening. Further investigation was, therefore, necessary and it was decided first to exclude the possibility of patent ductus arteriosus by an aortogram. For that purpose she was admitted to Green Lane Hospital one morning and the following is the sequence of events for that day: At 11 a.m., through a misunderstanding, 100 mg. of anthisan were given by mouth. At 12.30 p.m. an intradermal sensitivity test using 0·1 ml. of vasiodone (M & B) was followed immediately by an intravenous sensitivity test using 1 ml. of the same reagent. It was noted that according to the makers' instructions up to 3 ml. might be injected intravenously as a test dose, the absence of any reaction within two minutes indicating that the full dose of 40 ml. might then be given with safety. As, however, we were not quite ready to proceed with the aortogram the full dose of the drug was not actually given. Twenty minutes later, at 12.50 p.m., there was a sudden collapse with cyanosis and unconsciousness followed by convulsions. The breathing became stertorous and irregular and there was marked cutaneous congestion. The pulse rate rose to 140 a minute and became irregular and the blood pressure rose to 180/90. The convulsions were at first left-sided involving face, arm, and leg, but later they became generalized and in a few instances were purely right-sided. Later they reverted to the purely left-sided form. The abdominal reflexes disappeared, the plantar responses became extensor, and the tendon reflexes became exaggerated. Carpopedal spasm also developed and there was urinary incontinence. Ten minims of adrenalin, 1 in 1000, were given immediately

at the onset of the attack and a further six minims were given at 1.5 p.m. This was followed quickly by 15 ml. of 50 per cent glucose solution intravenously and 10 ml. of 15 per cent magnesium sulphate solution intramuscularly. At 2.30 p.m. lumbar puncture showed a cerebrospinal fluid pressure of more than 300 mm. of water, reduced to 250 mm. on removal of 15 ml. of fluid. At 3.30 p.m. 200 mg. of anthisan were given per rectum and a further 100 mg. together with prominal and phenobarbital were given four-hourly by stomach tube. Frequent lumbar punctures and further intramuscular injections of 15 per cent magnesium sulphate failed to keep down the pressure of the cerebrospinal fluid: for though the pressure fell considerably with every puncture, it quickly rose again to very high levels. No treatment was of any avail and although convulsions ceased on the second day the coma gradually deepened and the patient died at 7.43 p.m., three days after the injection of vasiodone.

*Necropsy* was performed by Dr. J. F. Burton and the relevant findings are given below.

The exterior of the brain was moderately congested and the convolutions were flattened. On section a few subcortical petechial hæmorrhages varying in diameter up to a few millimetres were dispersed chiefly over the temporal regions. No other gross abnormality was seen. Histological studies revealed focal hæmorrhages without cellular infiltration of adjacent normal brain tissue. The cerebral blood vessels appeared normal.

The thymus appeared normal. The heart was enlarged due to hypertrophy of both ventricles, chiefly the left. Aortic, mitral, pulmonary, and tricuspid valves appeared normal. The interatrial septum was deficient, there being a large oval foramen and a number of smaller orifices. The aorta and pulmonary artery were of normal dimensions and the ductus arteriosus was closed.

The liver, spleen, and kidneys were deeply congested but otherwise appeared normal. Histologically, the liver parenchyma, apart from slight vacuolation, appeared normal; the kidneys were congested and showed only slight tubular autolytic changes.

The necropsy diagnosis was multiple interatrial septal defects and acute anaphylaxis.

## Discussion

This child, who had previously shown no convulsive tendencies, collapsed with coma and convulsions 20 minutes after receiving unusually small sensitivity test doses of vasiodone. She had never previously had this or any similar drug. Family history of allergy was at first denied by the parents, but subsequent interrogation revealed a strong allergic history on both sides. The child herself had never suffered from asthma or hay fever but was susceptible to slight rashes which may have been due to food allergy. In view of its suddenness and severity the reaction must be regarded as anaphylactic. Such a response would be expected immediately after the administration of the drug and it is suggested that the delay of 20 minutes was due to the preceding dose of anthisan. That the severity of the reaction could have been in any way due to the anthisan seems incredible: for its use before the main dose of vasiodone has been our routine practice for many months, during which period there have been no other allergic reactions. Another interesting feature of this case was the hypertrophy of the left ventricle which was not accounted for by hypertension, aortic stenosis, or tricuspid atresia and was quite contrary to the usual finding in cases of auricular septal defect. This unexpected necropsy finding did not, however, appear to play any part in the anaphylactic reaction or death of the patient.

## Summary and Conclusions

A case of delayed fatal anaphylactic reaction to a small test dose of vasiodone is described, and measures for the safer administration of intravenous radio-opaque substances are discussed. The importance (*a*) of enquiring closely for an allergic family history, (*b*) of giving a very small initial test dose of the drug, and (*c*) of making a correct use of antihistamine drugs is emphasized.

For the safer administration of vasiodone and similar radio-opaque substances for intra-vascular use the following precautions should be observed.

(*a*) There must be a careful enquiry for a personal and family history of allergy, and if there is a strong allergic history these drugs must not be used.

(*b*) Sensitivity tests should be carried out as follows. A very small initial dose such as 0·1 ml. of the solution should be injected intravenously and a drop should then be instilled into the eye. Owing to chemical irritation these substances are not suitable for intra-dermal tests. If after half an hour there is no reaction indicating sensitivity, a further test dose of 1·5 ml. should be injected intravenously. If after a further half hour there is still no reaction the full dose may be given under cover of an anti-histamine drug; but experience may show that when no antihistamine drug has been given a much shorter period will suffice.

(*c*) Antihistamine drugs must be used correctly. The giving of antihistamine drugs before sensitivity tests, as was done inadvertently in this case, may so delay the sensitivity reaction as to give an apparently negative result when there is in fact, extreme sensitivity to the drug. Their use before such tests is, therefore, not only useless but may be dangerously misleading. There is, however, good reason to believe that antihistamine drugs, given about an hour before the main dose of the radio-opaque substance, are of real protective value and should, we believe, be thus used in every case.